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EXPEDITED REVIEWS

Dietary Linolenic Acid and Adjusted QT and JT Intervals in the National Heart, Lung, and Blood Institute Family Heart Study

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OBJECTIVES The goal of this study was to examine whether higher consumption of total linolenic acid was associated with rate-adjusted QT and JT intervals (QTrr and JTrr, respectively).

BACKGROUND Higher intake of fish omega-3 fatty acids and plant omega-3 such as alpha-linolenic acid is associated with lower risk of myocardial infarction. While long-chain omega-3 can inhibit ventricular arrhythmia, it is not known whether alpha-linolenic acid influences ventricular repolarization.

METHODS We studied 3,642 subjects from the National Heart, Lung, and Blood Institute Family Heart study who were free of myocardial infarction, left ventricular hypertrophy, pacemaker, and with QRS <120 ms. We used the 95th percentile of the gender-specific distribution of QTrr and JTrr to define abnormally prolonged repolarization. Within each gender, we created age- and energy-adjusted tertiles of linolenic acid and used regression models for analyses.

RESULTS Mean age was 50 years, and average intake of total linolenic acid was 0.74 g/day. There was an inverse association between consumption of linolenic acid and QTrr and JTrr (p for trend 0.001 and 0.0005, respectively). From the lowest (reference) to the highest gender-, age-, and energy-adjusted tertile of linolenic acid, multivariable adjusted odds ratios for prolonged QTrr were 1.0, 0.74 (95% confidence interval [CI] 0.57 to 0.96), and 0.59 (95% CI 0.44 to 0.77), respectively (p for trend 0.0003). Corresponding values for JTrr were 1.0, 0.73 (95% CI 0.52 to 1.03), and 0.59 (95% CI 0.40 to 0.87), respectively (p for trend 0.009). Exclusion of subjects taking drugs known to influence QT did not influence this association.

CONCLUSIONS Higher intake of dietary linolenic acid might be associated with a reduced risk of abnormally prolonged repolarization in men and women. (J Am Coll Cardiol 2005;45:1716–22)

Coronary artery disease (CAD) remains the leading cause of death in the U.S. While several studies have demonstrated the beneficial effects of dietary linolenic acid on myocardial infarction (1–5), limited data are available on possible underlying physiologic mechanisms. Reducing inflammation (6) and lowering triglycerides (7,8) and, perhaps, blood pressure (9) have been suggested as possible pathways. The role of linolenic acid on ventricular repolarization in humans has not been investigated. A small percentage of linolenic acid can be converted to long-chain omega-3 fatty acids such as eicosapentaenoic fatty acid (EPA) and, in lesser amounts, to docosahexaenoic acid (DHA) (10). Both EPA and DHA have been shown to reduce the risk of sudden cardiac death, possibly through antiarrhythmic effects (11,12). In an animal model, EPA and DHA prevented ventricular fibrillation compared with a control group (13). To date, no study has investigated whether dietary linolenic acid influences the ventricular repolarization phase in humans as measured by rate-adjusted QT and JT intervals (QTrr and JTrr, respectively) (14,15). Linoleic acid—an omega-6 fatty acid—competes with linolenic acid as substrates for desaturase and elongase enzymes. Because the Western diet is rich in linoleic acid, it has been suggested that a lower ratio of linoleic/linolenic acid (e.g., below 6) would maximize the conversion of linolenic acid to DHA (16). Dietary linolenic acid in foods is predominantly alpha-form, and a small amount of gamma-form is found mostly in fatty meat. Dietary linolenic acid is found

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Abbreviations and Acronyms

AA = arachidonic acid
CAD = coronary artery disease
CI = confidence interval
DHA = docosahexaenoic acid
ECG = electrocardiogram/electrocardiographic
EPA = eicosapentaenoic acid
JTrr = rate-adjusted JT interval as JT − 176 · [(60/HR) − 1] + 14 for men (HR = heart rate)
NHLBI = National Heart, Lung, and Blood Institute
QTc = rate-adjusted QT interval as $QT/RR^{1/2}$
QTrr = rate-adjusted QT interval as QT − 185 · [(60/HR) − 1] + 6 for men (HR = heart rate)

mainly in flaxseed, linseed, and canola oil, and, to a lesser extent, in soybean oil and green leafy vegetables (16).

We used data collected on 3,642 Caucasian participants of the National Heart, Lung, and Blood Institute (NHLBI) Family Heart study to assess whether dietary consumption of higher amounts of total linolenic acid (alpha- and gamma-form) was associated with QTrr and JTrr. In addition, we evaluated whether such association was modified by the ratio of linoleic-to-linolenic fatty acid.

METHODS

Study population. Subjects in this project were participants of the NHLBI Family Heart study. A detailed description of the NHLBI Family Heart study has been published (17). Briefly, families in the study had been chosen randomly (a random group n = 2,673) or based on a higher than expected risk of CAD from previously established population-based cohort studies (a high-risk group n = 3,037). A family risk score, which related the family's age- and gender-specific incidence of CAD to that expected in the general population (18), was used to identify families for the high-risk group. Of the 5,710 Caucasian subjects, we excluded 2,068 from the main analyses for the following reasons: 1) missing data on electrocardiogram (ECG) (n = 21), or on dietary linolenic acid (n = 827), or covariates (n = 119); 2) unreliable food frequency questionnaire (n = 149); 3) energy intake outside a priori ranges (n = 140); 4) myocardial infarction (n = 498) or major ventricular conduction defect (n = 308); and 5) QRS interval above 120 ms (n = 6).We did not have an adequate sample on non-Caucasians (n = 265) for separate analyses. Each participant gave informed consent, and the study protocol was reviewed and approved by each of the participating institutions.

Dietary assessment. We used a staff-administered semiquantitative food frequency questionnaire (19) to obtain data on dietary linolenic acid and other nutrients. The reproducibility and validity of this food frequency questionnaire have been described previously (20). Nutrients were obtained by multiplying the frequency of consumption of an item by the nutrient content of specified portions. Composition values for total linolenic acid and other nutrients were obtained from the Harvard University Food Composition Database derived from U.S. Department of Agriculture sources (21) and manufacturer information.

ECG methodology. All ECGs in the study were recorded using strictly standardized methods for ECG acquisition and processing. These methods have been described previously (22). Briefly, during the clinic visit, standard 12-lead ECGs were recorded using MAC-PC electrocardiographs (Marquette Electronics, Inc., Milwaukee, Wisconsin), and 10-s records were digitized using a sampling rate of 250 samples/s per lead. All QT measurements were visually verified, and occasional errors were corrected using interactive graphics terminals. The QT and JT intervals were rate-adjusted as a linear function of the RR interval using the algorithms described by Rautaharju et al. (15): QTrr = QT − 185 · (60/heart rate − 1) + [6 ms in men] and JTrr = JT − 176 · (60/heart rate − 1) + [14 ms in men], where JT = QT − QRS. This method of adjustment eliminates the strong residual correlation between the adjusted QT and heart rate observed repeatedly for the Bazett's QTc (23–25).

Other variables. Resting blood pressure was measured three times on sitting participants after a 5-min rest using a random zero sphygmomanometer by trained technicians. Information on cigarette smoking, alcohol intake, education, and level of physical activity during the previous year was obtained by interview. Diabetes mellitus was present if a subject was taking hypoglycemic agents, or if a physician had told him/her that he/she has diabetes mellitus, or if fasting glucose levels were above 7.0 mmol/l. Prevalent CAD was assessed by self-reported history of myocardial infarction, percutaneous transluminal coronary angioplasty, or coronary artery bypass graft. Use of digoxin, diuretic, antiarrhythmic drugs, and other prescription drugs were assessed through medication inventory.

Statistical analyses. Because higher energy intake is associated with higher linolenic acid and energy intake and dietary patterns differ between men and women and by age, we created gender-, age-, and energy-specific tertiles of linolenic acid. Within each gender, we created four-year age groups (seven categories) and quintiles of energy intake. Then, within each of the 35 groups, we created tertiles of linolenic acid (referred to as gender-, age-, and energy-specific tertiles of linolenic acid). To estimate adjusted mean values of QTrr and JTrr, we used generalized estimating equations to account for familial clustering and confounding factors. The minimal adjusted model controlled for age, body mass index, systolic and diastolic blood pressure, and serum potassium. The full model also controlled for diabetes mellitus, exercise, class Ia and class III antiarrhythmic drugs, and other drugs known to prolong QT intervals or increase the risk of Torsades de Pointes (i.e., antipsychotic, antimalarial, macrolide antibiotics, opiate agonist, and so on). Further adjustment for center, education, diuretic use, risk group (random vs. high-risk group), long-chain omega-3 fatty acids, and waist-hip ratio did not alter the results (data

not shown). We also used the 95th percentile of the gender-specific distribution of QTrr (446.9 for men and 455.0 for women) and JTrr (359.0 for men and 363.7 for women) to define abnormal QTrr and abnormal JTrr and used a generalized estimating equation to compute the prevalence odds ratios. In addition, we used linolenic acid as a continuous variable and related it to QTrr and JTrr. We conducted sensitivity analyses by: 1) excluding subjects who were using digoxin or antiarrhythmic drugs; and 2) using subjects previously excluded in the initial analyses. Because linoleic and linolenic acids are competitive substrate for desaturase, we assessed whether the linoleic/linolenic ratio modified the association through: 1) stratified analyses using gender-specific median values of linolenic acid to create two groups; and 2) including main effects and product term in the regression model. Alpha level was set at 0.05, and all analyses were completed using windows SAS version 5.1.2, release 8.02 (SAS Institute, Cary, North Carolina).

RESULTS

Characteristics of participants. Of the 3,642 Caucasian participants included in the analyses, 1,477 were men and 2,165 were women. The mean age was 48.6 ± 13.4 years for men and 51.1 ± 13.4 years for women. The average daily consumption of total dietary linolenic acid was 0.81 ± 0.35 g for men (range 0.21 to 3.48 g/day) and 0.69 ± 0.29 g for women (range 0.13 to 2.45 g/day). Table 1 presents the baseline characteristics by gender-, age-, and energy-adjusted tertiles of dietary linolenic acid.

Association between dietary linolenic acid and QTrr and JTrr intervals. Dietary linolenic acid was inversely associated with QTrr in men in a multivariable adjusted model (p for linear trend 0.0009) (Table 2). In women, a nonstatistically significant inverse association between dietary linolenic acid and QTrr was observed (p for trend 0.12) (Table 2). In a multivariable model, both men and women showed an inverse association between linolenic acid and JTrr in a dose-response fashion (p for linear trend 0.002 for men and 0.04 for women) (Table 2). We observed a similar association using dietary linolenic acid as a continuous variable. For men and women combined, the regression coefficients (SE) for QTrr were −0.5479 (0.1888) for the crude model and −0.835 (0.3061) for the multivariate-adjusted regression model. Corresponding values for JTrr were −0.4945 (0.2437) for the crude and −0.9994 (0.4224) for the multivariable model.

There was evidence for a reduced risk for the prolonged repolarization in both men and women. From the lowest to

Table 1. Characteristics of the 3,642 Participants of the NHLBI Family Heart Study According to Gender-, Age-, and Energy-Adjusted Tertiles of Dietary Linolenic Acid*

	Tertiles of Linolenic Acid [Median, g/day]					
	Men			Women		
Characteristics	1 (Low) [0.58] (n = 484)	2 [0.78] (n = 501)	3 (High) [0.96] (n = 492)	1 (Low) [0.50] (n = 708)	2 [0.64] (n = 749)	3 (High) [0.85] (n = 708)
Age (yrs)	47.8 ± 13.6	49.2 ± 13.3	48.9 ± 13.2	50.6 ± 13.7	51.4 ± 13.3	51.3 ± 13.2
Body mass index (kg/m^2)	27.2 ± 4.2	27.8 ± 4.5	28.0 ± 4.8	26.5 ± 5.7	27.1 ± 6.0	27.6 ± 6.6
Waist-hip ratio	0.95 ± 0.08	0.96 ± 0.07	0.95 ± 0.07	0.87 ± 0.10	0.87 ± 0.09	0.88 ± 0.09
DHA + EPA (g)	0.23 ± 0.22	0.24 ± 0.25	0.21 ± 0.17	0.21 ± 0.19	0.25 ± 0.24	0.22 ± 0.20
Linoleic/linolenic ratio	11.9 ± 4.4	10.6 ± 3.3	9.4 ± 2.8	11.6 ± 5.2	10.0 ± 3.4	8.7 ± 2.6
Energy intake (KJ)	7,764 ± 2,532	8,041 ± 2,627	8,438 ± 3,082	6,576 ± 2,173	6,728 ± 2,249	7,040 ± 2,447
Blood pressure						
Diastolic (mm Hg)	71.5 ± 10.3	72.1 ± 9.2	71.6 ± 9.9	66.1 ± 9.7	67.1 ± 9.7	67.7 ± 9.5
Systolic (mm Hg)	118.5 ± 15.9	118.5 ± 15.3	117.1 ± 15.4	113.0 ± 17.6	113.1 ± 17.4	114.1 ± 18.0
Potassium (mmol/l)	4.2 ± 0.33	4.3 ± 0.30	4.3 ± 0.3	4.1 ± 0.3	4.1 ± 0.3	4.1 ± 0.3
Exercise (min/day)	38.4 ± 47.8	34.2 ± 38.3	34.4 ± 41.2	27.5 ± 35.0	24.1 ± 32.1	21.9 ± 29.9
Random sample (%)	52.5	54.7	52.2	47.7	48.7	48.7
Antiarrhythmic drug class Ia or II (%)	1.5	1.0	1.6	2.4	3.5	2.7
Digoxin use (%)	1.5	1.4	0.6	1.4	0.7	1.3
Use of non-potassium sparing diuretic (%)	3.5	2.4	2.6	4.1	5.1	5.5
Use of other drugs known to prolong QT interval (%)	1.2	1.2	1.6	1.1	1.5	2.5
Education (%)						
≤High school	26.0	27.9	28.8	34.2	36.2	43.0
Some college	9.1	12.0	13.1	14.7	12.8	10.6
College graduate	64.9	60.1	58.1	51.1	51.1	46.4
Hypertension (%)	13.6	13.0	11.2	11.3	11.3	12.0
Diabetes mellitus (%)	2.1	4.6	5.5	3.5	5.6	4.5

*Values expressed as mean ± SD, unless specified otherwise.
DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; NHLBI = National Heart, Lung, and Blood Institute.

Table 2. Crude and Adjusted Mean Values ± SE of the Rate-Adjusted QT and JT Intervals by Gender and Tertiles of Dietary Linolenic Acid in 3,642 Participants of the NHLBI Family Heart Study

Age- and Energy-Adjusted Tertiles of Dietary Linolenic Acid [Median]	n	Mean ± SE of QTrr			Mean ± SE of JTrr		
		Crude	Model 1*	Model 2†	Crude	Model 1*	Model 2†
Men							
1 [0.58 g/day] (low)	484	418.5 ± 0.9	419.0 ± 0.8	419.1 ± 0.8	328.2 ± 0.9	328.7 ± 0.9	328.8 ± 0.9
2 [0.78 g/day]	501	417.0 ± 0.8	416.8 ± 0.8	416.8 ± 0.8	327.0 ± 0.9	326.7 ± 0.8	326.7 ± 0.9
3 [0.96 g/day] (high)	492	415.6 ± 0.9	415.3 ± 0.8	415.2 ± 0.8	325.5 ± 0.9	325.2 ± 0.9	325.1 ± 0.9
p value for linear trend		0.02	0.002	0.0009	0.03	0.005	0.002
Women							
1 [0.50 g/day] (low)	708	424.7 ± 0.7	425.2 ± 0.7	425.3 ± 0.7	333.8 ± 0.8	334.1 ± 0.7	334.3 ± 0.7
2 [0.64 g/day]	749	424.6 ± 0.7	424.4 ± 0.7	424.4 ± 0.7	332.9 ± 0.7	332.7 ± 0.7	332.7 ± 0.7
3 [0.85 g/day] (high)	708	424.1 ± 0.7	423.8 ± 0.7	423.7 ± 0.7	332.3 ± 0.8	332.1 ± 0.7	332.1 ± 0.7
p value for linear trend		0.52	0.18	0.12	0.15	0.05	0.04
Men and women combined							
1 [0.53 g/day] (low)	1,192	422.2 ± 0.6	422.6 ± 0.5	422.8 ± 0.5	331.5 ± 0.6	331.9 ± 0.6	332.1 ± 0.6
2 [0.69 g/day]	1,250	421.6 ± 0.6	421.4 ± 0.5	421.3 ± 0.5	330.5 ± 0.6	330.3 ± 0.5	330.3 ± 0.5
3 [0.89 g/day] (high)	1,200	420.6 ± 0.6	420.4 ± 0.5	420.3 ± 0.5	329.5 ± 0.6	329.4 ± 0.6	329.3 ± 0.6
p value for linear trend		0.04	0.005	0.001	0.013	0.002	0.0005

QTrr = QT − 185 · [(60/HR) − 1] + 6 for men and QT − 185 · [(60/HR) − 1] for women, where HR is heart rate. JTrr = JT − 176 · [(60/HR) − 1] + 14 for men and JT − 176 · [(60/HR) − 1] for women. *Adjusted for age, body mass index, systolic and diastolic blood pressure, and serum potassium. †Additional adjustment for energy intake, diabetes mellitus, physical activity, class Ia and class III anti-arrhythmic drugs, and other drugs known to prolong QT intervals. The combined group also adjusts for gender.

JTrr = rate-adjusted JT interval; NHBLI = National Heart, Lung, and Blood Institute; QTrr = rate-adjusted QT interval.

the highest tertile of linolenic acid, multivariable adjusted prevalence odds ratios for prolonged repolarization based on QTrr were 1.0 (reference), 0.81 (95% confidence intervals [CI] 0.46 to 1.44), and 0.51 (95% CI 0.27 to 0.98), respectively, for men (p for trend 0.04) (Table 3). Corresponding values for women were 1.0, 0.71 (95% CI 0.53 to 00.95), and 0.60 (95% CI 0.44 to 0.82), respectively (p for trend 0.003) (Table 3). Similar reduced risk of prolonged repolarization using JTrr was observed, and the results were stronger in women than in men (Table 4). In both men and women combined, the risk of abnormally prolonged repolarization was 41% lower in the highest tertile of linolenic acid compared with the lowest tertile in a multivariable adjusted model (Table 4).

The ratio of linoleic-to-linolenic acid did not influence the results, and there was no evidence for interaction between linoleic and linolenic acid on abnormal QTrr (p = 0.21) or JTrr (p = 0.23).

Sensitivity analyses. Exclusion of subjects currently receiving digoxin and/or antiarrhytmic drugs did not change the results. From the lowest to the highest tertile of linolenic acid, multivariable adjusted odds ratios for prolonged repolarization using QTrr in the combined data set were 1.0 (reference), 0.75 (95% CI 0.57 to 0.98), and 0.61 (95% CI

Table 3. Crude and Adjusted Odds Ratios (95% Confidence Intervals) for Abnormal Rate-Adjusted QT According to Gender-, Age-, and Energy-Adjusted Tertiles of Dietary Linolenic Acid in 3,642 Participants of the NHLBI Family Heart Study*

Age- and Energy-Adjusted Tertiles of Dietary Linolenic Acid [Median]	Cases/n	OR (95% CI) for Abnormal QTrr		
		Crude	Model 1†	Model 2‡
Men				
1 [0.58 g/day] (low)	30/484	1.0	1.0	1.0
2 [0.78 g/day]	27/501	0.86 (0.50–1.50)	0.81 (0.46–1.42)	0.81 (0.46–1.44)
3 [0.96 g/day] (high)	17/492	0.54 (0.29–1.02)	0.50 (0.26–0.94)	0.51 (0.27–0.98)
p value for linear trend		0.06	0.03	0.04
Women				
1 [0.50 g/day] (low)	120/708	1.0	1.0	1.0
2 [0.64 g/day]	102/749	0.77 (0.58–1.03)	0.72 (0.54–0.97)	0.71 (0.53–0.95)
3 [0.85 g/day] (high)	88/708	0.69 (0.51–0.94)	0.63 (0.46–0.86)	0.60 (0.44–0.82)
p value for linear trend		0.02	0.005	0.003
Men and women combined				
1 [0.53 g/day] (low)	150/1,192	1.0	1.0	1.0
2 [0.69 g/day]	129/1,250	0.80 (0.62–1.03)	0.75 (0.58–0.98)	0.74 (0.57–0.96)
3 [0.89 g/day] (high)	105/1,200	0.67 (0.51–0.87)	0.61 (0.46–0.81)	0.59 (0.44–0.78)
p value for linear trend		0.004	0.005	0.0003

QTrr = QT − 185 · [(60/HR) − 1] + 6 for men and QT − 85 · [(60/HR) − 1] for women, where HR is heart rate. *Abnormal QTrr is defined as a QTrr value greater than 95th percentile of the gender-specific distribution. †Adjusted for age, body mass index, systolic and diastolic blood pressure, and serum potassium. ‡Additional adjustment for energy intake, diabetes mellitus, physical activity, class Ia and class III anti-arrhythmic drugs, and other drugs known to prolong QT intervals. The combined group also adjusts for gender.

CI = confidence interval; OR = odds ratio; other abbreviations as in Table 2.

Table 4. Crude and Adjusted Odds Ratios (95% Confidence Intervals) for Abnormal Rate-Adjusted JT by Gender-, Age-, and Energy-Adjusted Tertiles of Dietary Linolenic Acid in 3,642 Participants of the NHLBI Family Heart Study*

Age- and Energy-Adjusted Tertiles of Dietary Linolenic Acid [Median]	Cases/n	OR (95% CI) for Abnormal JTrr		
		Crude	Model 1†	Model 2‡
Men				
1 [0.58 g/day] (low)	29/484	1.0	1.0	1.0
2 [0.78 g/day]	24/501	0.79 (0.45–1.38)	0.77 (0.44–1.36)	0.77 (0.44–1.36)
3 [0.96 g/day] (high)	20/492	0.66 (0.36–1.20)	0.68 (0.37–1.25)	0.68 (0.36–1.27)
p value for linear trend		0.18	0.21	0.22
Women				
1 [0.50 g/day] (low)	45/708	1.0	1.0	1.0
2 [0.64 g/day]	36/749	0.74 (0.49–1.35)	0.71 (0.46–1.08)	0.70 (0.46–1.08)
3 [0.85 g/day] (high)	27/708	0.58 (0.35–0.96)	0.54 (0.32–0.90)	0.53 (0.32–0.89)
p value for linear trend		0.04	0.02	0.02
Men and women combined				
1 [0.53 g/day] (low)	74/1,192	1.0	1.0	1.0
2 [0.69 g/day]	60/1,250	0.76 (0.54–1.07)	0.73 (0.52–1.03)	0.73 (0.52–1.03)
3 [0.89 g/day] (high)	47/1,200	0.62 (0.42–0.90)	0.59 (0.40–0.88)	0.59 (0.40–0.87)
p value for linear trend		0.014	0.009	0.009

JTrr = JT − 176 · [(60/HR) − 1] + 14 for men and JT − 176 · [(60/HR) − 1] for women; where HR is heart rate. *Abnormal QTrr is defined as a QTrr value greater than 95th percentile of the gender-specific distribution. †Adjusted for age, body mass index, systolic and diastolic blood pressure, and serum potassium. ‡Additional adjustment for energy intake, diabetes mellitus, physical activity, class Ia and class III anti-arrhythmic drugs, and other drugs known to prolong QT intervals. The combined group also adjusts for gender.

Abbreviations as in Tables 2 and 3.

0.45 to 0.82), respectively (p for trend 0.0012). Corresponding values were 1.0, 0.64 (95% CI 0.45 to 0.91), and 0.53 (95% CI 0.35 to 0.80), respectively, using JTrr (p for trend 0.003). In a sample (n = 4,504) that included subjects excluded in the initial analyses (i.e., prevalent CAD, left ventricular hypertrophy, and so on), the observed association persisted (i.e., p for trend 0.0017 using QTrr to define abnormal repolarization), and further adjustment for left ventricular hypertrophy, T-negativity, ST-segment depression/elevation did not change the results.

DISCUSSION

In this cross-sectional study, higher intake of dietary total linolenic acid (alpha- and gamma-form) was inversely associated with heart-rate–adjusted QT and JT intervals in a dose-response manner in both men and women. This association was not modified by the ratio of n-6 to n-3 fatty acids.

n-3 fatty acids and arrhythmia. While epidemiologic studies have shown the beneficial effects of linolenic acid on fatal and nonfatal CAD (1–5), triglycerides (8), and carotid wall thickness (26), no data are available on the effects of linolenic acid on myocardial repolarization in humans. Evidence of beneficial effects of EPA and DHA on ventricular arrhythmia has been shown in animal models and in humans. Infusion of EPA (12,13), DHA (12,13), and alpha-linolenic acid (12) in dogs was associated with a significant reduction in ventricular fibrillation. Rats fed with a tuna fish oil diet had a significantly lower incidence rate and severity of arrhythmias and lower risk of ventricular fibrillation compared with rats on a diet enriched with sunflower oil (27). In a study of monkeys, fish oil was associated with significantly raised ventricular fibrillation threshold (33.3 mA) compared with sunflower oil (14.3 mA) after a 16-week intervention (28). Siscovick et al. (29) demonstrated that, compared with no intake of dietary EPA and DHA, monthly intake of 5.5 g of n-3 fatty acid was associated with a 50% reduction in the risk of primary cardiac arrest in 334 patients. In a randomized control trial, a diet rich in EPA and DHA was associated with a 48% decrease in ventricular premature complexes compared to only 25% reduction in the placebo group (sunflower oil) after 16 weeks of intervention (30). Nevertheless, little is known about the relation between dietary linolenic acid and ventricular repolarization or arrhythmia. The only evidence showing antiarrhythmic effects of alpha-linolenic acid has been provided from animal study. In a dog model of cardiac sudden death, alpha-linolenic acid infusion prevented fatal ventricular fibrillation in six of eight dogs (12), an effect similar to infusion of DHA or EPA in the same study. To our knowledge, no previous study has examined the relation between dietary linolenic acid and heart-rate–adjusted QT or JT intervals.

Physiologic mechanisms. Modification of the eicosanoid system by dietary fatty acids is one of the suggested mechanisms by which EPA and DHA protect against ventricular arrhythmia. The Western diet is rich in linoleic acid, which is a precursor of arachidonic acid (AA); AA is metabolized to generate (n-2) series of prostanoids such as thromboxane A_2 and leukotrienes. Alpha-linolenic acid is a precursor of prostaglandin I_3 (a vasodilator) and thromboxane A_3, which is less active (9). A limited amount of linolenic acid is converted to EPA in vivo; EPA competes with AA as a substrate for cyclooxygenase, thus inhibiting the production of thromboxane A_2 that causes vasoconstrictor and platelet aggregation. A reduced ratio of AA/EPA favors the production of (n-3) series of prostanoids and less

thromboxane A_2 and, thus, reduces the risk of ventricular fibrillation and cardiac arrest (31). Another possible mechanism is the modulation of L-type calcium channels in the sarcolemma of cardiac myocytes by DHA (32). However, additional research is needed to elucidate biologic mechanisms underlying antiarrhythmic effects of n-3 fatty acids.

Other investigators have suggested that a diet rich in n-3 fatty acids (such as linolenic acid) could suppress plasma levels of metabolites of linoleic acid such as thromboxane A_2, which stimulates vasoconstriction and platelet aggregation (33). This has been the basis to favor a lower ratio of linoleic-to-linolenic acid (below 6). In the present study, the association between linolenic acid and QT intervals was not modified by the ratio of linoleic-to-linolenic acid.

Study limitations. In the present study, nutrients were derived from a food frequency questionnaire that has been shown to underestimate energy intake when compared with the doubly-labeled water technique (34). Therefore, our estimate of daily intake of linolenic acid and other nutrients might have been biased. We did not have data separately on alpha- and gamma-linolenic acid. In addition, the cross-sectional design of our study limits our ability to infer causality between linolenic acid intake and QT/JT. However, the large sample size, the availability of data on several risk factors, the wide range of age and linolenic acid, the consistency of our findings with other published reports, and the multicenter design are strengths of our study.

In conclusion, our data suggest that higher consumption of dietary linolenic acid is associated with a reduced risk of prolonged repolarization in both men and women. While this might be one of the underlying mechanisms by which dietary linolenic acid decrease the risk of cardiovascular disease, future studies are needed to confirm our findings.

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REFERENCES

1. de Lorgeril M, Renaud S, Mamelle N, et al. Mediterranean alpha-linolenic acid-rich diet in secondary prevention of coronary heart disease. Lancet 1994;343:1454–9.
2. Hu FB, Stampfer MJ, Manson JE, et al. Dietary intake of alpha-linolenic acid and risk of fatal ischemic heart disease among women. Am J Clin Nutr 1999;69:890–7.
3. Djoussé L, Pankow JS, Eckfeldt JH, et al. Relation between dietary linolenic acid and coronary artery disease in the National Heart, Lung, and Blood Institute Family Heart study. Am J Clin Nutr 2001;74:612–9.
4. Baylin A, Kabagambe EK, Ascherio A, Spiegelman D, Campos H. Adipose tissue alpha-linolenic acid and nonfatal acute myocardial infarction in Costa Rica. Circulation 2003;107:1586–91.
5. Rastogi T, Reddy KS, Vaz M, et al. Diet and risk of ischemic heart disease in India. Am J Clin Nutr 2004;79:582–92.
6. Rallidis LS, Paschos G, Liakos GK, Velissaridou AH, Anastasiadis G, Zampelas A. Dietary alpha-linolenic acid decreases C-reactive protein, serum amyloid A and interleukin-6 in dyslipidaemic patients. Atherosclerosis 2003;167:237–42.
7. Kris-Etherton PM, Yu S. Individual fatty acid effects on plasma lipids and lipoproteins: human studies. Am J Clin Nutr 1997;65:1628S–44S.
8. Djoussé L, Hunt CS, Arnett DK, Province MA, Eckfeldt JH, Ellison RC. Dietary linolenic acid is inversely associated with plasma triacylglycerol: the National Heart, Lung, and Blood Institute Family Heart study. Am J Clin Nutr 2003;78:1098–102.
9. Salonen JT, Salonen R, Ihanainen M, et al. Blood pressure, dietary fats, and antioxidants. Am J Clin Nutr 1988;48:1226–32.
10. Gerster H. Can adults adequately convert alpha-linolenic acid (18:3n-3) to eicosapentaenoic acid (20:5n-3) and docosahexaenoic acid (22:6n-3)? Int J Vit Nutr Res 1988;68:159–73.
11. Kang JX, Leaf A. Prevention of fatal cardiac arrhythmias by polyunsaturated fatty acids. Am J Clin Nutr 2000;71:202S–7S.
12. Billman GE, Kang JX, Leaf A. Prevention of sudden cardiac death by dietary pure omega-3 polyunsaturated fatty acids in dogs. Circulation 1999;99:2452–7.
13. Billman GE, Hallaq H, Leaf A. Prevention of ischemia-induced ventricular fibrillation by omega 3 fatty acids. Proc Natl Acad Sci U S A 1994;91:4427–30.
14. Rautaharju PM, Zhang ZM. Linearly scaled, rate-invariant normal limits for QT interval: eight decades of incorrect application of power functions. J Cardiovasc Electrophysiol 2002;13:1211–8.
15. Rautaharju PM, Zhang ZM, Prineas R, Heiss G. Assessment of prolonged QT and JT intervals in ventricular conduction defects. Am J Cardiol 2004;93:1017–21.
16. Kris-Etherton PM, Taylor DS, Yu-Poth S, et al. Polyunsaturated fatty acids in the food chain in the United States. Am J Clin Nutr 2000;71:179S–88S.
17. Higgins M, Province M, Heiss G, et al. NHLBI Family Heart study: objectives and design. Am J Epidemiol 1996;143:1219–28.
18. Hunt SC, Williams RR, Barlow GK. A comparison of positive family history definitions for defining risk of future disease. J Chronic Dis 1986;39:809–21.
19. Willett WC, Sampson L, Stampfer MJ, et al. Reproducibility and validity of a semiquantitative food frequency questionnaire. Am J Epidemiol 1985;122:51–65.
20. Rimm EB, Giovannucci EL, Stampfer MJ, Colditz GA, Litin LB, Willett WC. Reproducibility and validity of an expanded self-administered semiquantitative food frequency questionnaire among male health professionals. Am J Epidemiol 1992;135:1114–26.
21. US Department of Agriculture. Composition of Foods: Raw, Processed, and Prepared, 1963–1988. Agriculture handbook no. 8. Washington DC: U.S. Government Printing Office, 1989.
22. Hong Y, Rautaharju PM, Hopkins PN, et al. Familial aggregation of QT-interval variability in a general population: results from the NHLBI Family Heart study. Clin Genet 2001;59:171–7.
23. Kawataki M, Kashima T, Toda H, Tanaka H. Relation between QT interval and heart rate. Applications and limitations of Bazett's formula. J Electrocardiol 1984;17:371–5.
24. Rautaharju PM, Warren JW, Calhoun HP. Estimation of QT prolongation. A persistent, avoidable error in computer electrocardiography. J Electrocardiol 1990;23 Suppl:111–7.
25. Sagie A, Larson MG, Goldberg RJ, Bengtson JR, Levy D. An improved method for adjusting the QT interval for heart rate (the Framingham Heart study). Am J Cardiol 1992;70:797–801.
26. Djoussé L, Folsom AR, Province MA, Hunt SC, Ellison RC. Dietary linolenic acid and carotid atherosclerosis: the National Heart, Lung, and Blood Institute Family Heart study. Am J Clin Nutr 2003;77:819–25.
27. McLennan PL, Abeywardena MY, Charnock JS. Dietary fish oil prevents ventricular fibrillation following coronary artery occlusion and reperfusion. Am Heart J 1988;116:709–17.
28. McLennan PL, Bridle TM, Abeywardena MY, Charnock JS. Comparative efficacy of n-3 and n-6 polyunsaturated fatty acids in modulating ventricular fibrillation threshold in marmoset monkeys. Am J Clin Nutr 1993;58:666–9.
29. Siscovick DS, Raghunathan TE, King I, et al. Dietary intake and cell membrane levels of long-chain n-3 polyunsaturated fatty acids and the risk of primary cardiac arrest. JAMA 1995;274:1363–7.

30. Sellmayer A, Witzgall H, Lorenz RL, Weber PC. Effects of dietary fish oil on ventricular premature complexes. Am J Cardiol 1995;76: 974–7.
31. Coker SJ, Parratt JR, Ledingham IM, Zeitlin IJ. Evidence that thromboxane contributes to ventricular fibrillation induced by reperfusion of the ischaemic myocardium. J Mol Cell Cardiol 1982;14: 483–5.
32. Hallaq H, Smith TW, Leaf A. Modulation of dihydropyridine-sensitive calcium channels in heart cells by fish oil fatty acids. Proc Natl Acad Sci U S A 1992;89:1760–4.
33. Salonen R, Nikkari T, Seppanen K, et al. Effect of omega-3 fatty acid supplementation on platelet aggregability and platelet produced thromboxane. Thromb Haemost 1987;57:269–72.
34. Trabulsi J, Schoeller DA. Evaluation of dietary assessment instruments against doubly labeled water, a biomarker of habitual energy intake. Am J Physiol Endocrinol Metab 2001;281:E891–9.